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**The impact of upper-limb position on estimated central blood pressure waveforms**

**Running Title:** Central hemodynamic estimation

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27 **ABSTRACT**

28 Pulse wave analysis (PWA) utilizes arm blood pressure (BP) waveforms to estimate aortic  
 29 waveforms. The accuracy of central BP waveform estimation may be influenced by  
 30 assessment site local hemodynamics. This study investigated whether local hemodynamic  
 31 changes, induced via arm tilting  $\pm 30^\circ$  relative to heart level, affect estimated central  
 32 systolic BP (cSBP) and arterial wave reflection (central augmentation index, cAIx; aortic  
 33 backward pressure wave, Pb). In 20 healthy adults (26.7 y [SD 5.2], 10 F) brachial BP  
 34 waveforms were simultaneously recorded on experimental and control arms. The  
 35 experimental arm was randomly repositioned three times (heart level,  $-30^\circ$  heart level,  
 36  $+30^\circ$  heart level), while the control arm remained fixed at heart level. For the  
 37 experimental arm, arm repositioning resulted in a large (partial eta-squared  $>0.14$ ) effect  
 38 size (ES) change in SBP (ES=0.75,  $P<0.001$ ), cSBP (ES =0.81,  $P<0.001$ ), and cAIx (ES =0.75,  
 39  $P=0.002$ ), but not Pb (ES =0.06,  $P=0.38$ ). In the control arm, cAIx (ES =0.22,  $P=0.013$ ) but  
 40 not SBP or cSBP significantly changed. Change in experimental arm cSBP was partially  
 41 explained by brachial systolic blood velocity ( $P=0.026$ ) and mean diameter ( $P=0.012$ ),  
 42 while change in cAIx was associated with brachial retrograde blood velocity ( $P=0.020$ ) and  
 43 beta stiffness ( $P=0.038$ ). In conclusion, manipulation of assessment site local  
 44 hemodynamics, including the blood velocity profile and local arterial stiffness, had a large  
 45 effect on estimated cSBP and cAIx, but not Pb. These findings do not invalidate PWA  
 46 devices but do suggest that the accuracy of the estimated aortic pressure waveform is  
 47 dependent on stable peripheral hemodynamics.

48 **KEY WORDS:** posture; arterial stiffness; pulse wave analysis; central blood pressure;  
49 arterial wave reflection

## 50 INTRODUCTION

51 Pulse wave analysis (PWA) devices permit the estimation of central hemodynamic  
 52 properties, including arterial wave reflection (central augmentation index [cAIx], aortic  
 53 backward pressure wave [Pb]), and central systolic blood pressure (cSBP). Considering that  
 54 cSBP more closely reflects left ventricular and cerebrovascular load than brachial  
 55 pressure,<sup>1,2</sup> and is a more accurate marker of cardiovascular risk,<sup>2</sup> PWA is increasingly  
 56 attractive to epidemiologists and clinicians. However, the accuracy of central  
 57 hemodynamic estimates may be influenced by local hemodynamic changes.

58

59 Local pressure hemodynamics are influenced by gravitational changes, including small  
 60 variation in the assessment site level relative to the heart. Such variation may occur with  
 61 incorrect positioning of the arm, change in posture, or while using ambulatory devices.  
 62 Pucci *et al.*<sup>3</sup> examined the importance of gravitational changes by tilting the upper-limb  
 63 30° above and 30° below heart level during supine PWA assessments. This experimental  
 64 model is simple yet effective in that local hemodynamics are likely to be manipulated in  
 65 the absence of central hemodynamic changes. Pucci *et al.*<sup>3</sup> observed that peripherally  
 66 derived indexes of cSBP and cAIx appeared ‘older’ when the upper arm was raised and  
 67 ‘younger’ when the upper arm was lowered. These changes occurred in the experimental  
 68 arm despite no observable change in the fixed position (heart level) control arm,  
 69 suggesting that ‘changes’ to the estimated central waveform were likely an artifact of local  
 70 hemodynamic manipulation.

71

72 Unfortunately, Pucci *et al.*<sup>3</sup> did not measure important local hemodynamic properties,  
 73 such as blood flow and local arterial stiffness. Further, cAlx but not Pb was measured. cAlx  
 74 is known to be affected by the reflected wave transit time,<sup>4</sup> whereas Pb is thought to be  
 75 independent of the transit time<sup>5</sup> and has been demonstrated to be more resistant to  
 76 changes in posture.<sup>6–9</sup> Therefore, the primary objective of this study was to investigate the  
 77 effects of local hemodynamic manipulation, induced by tilting the arm +/-30 degrees  
 78 relative to heart level, on PWA estimated cSBP, cAlx and Pb. The secondary objective was  
 79 to determine the association between change in estimated cSBP, cAlx and Pb and change  
 80 in local hemodynamic properties (arterial stiffness, blood velocity/flow).

81

## 82 **METHODS**

83 This study is reported in accordance with STROBE (Strengthening the Reporting of  
 84 Observational Studies in Epidemiology) guidelines.<sup>10</sup>

85

## 86 **PARTICIPANTS**

87 Twenty young (18 – 40 y), healthy women (n=10) and men were recruited from a large  
 88 state university. A healthy population sample was recruited to mitigate the risk of age- or  
 89 disease-related influences on BP. Participants were excluded if they reported any known  
 90 cardio-metabolic disorders, were taking medications known to affect cardiovascular  
 91 function, or reported cigarette smoking. Ethical approval was obtained from the University

of North Carolina at Chapel Hill institutional review board, and all participants provided written informed consent prior to participating in the study.

## EXPERIMENTAL DESIGN

Participants were familiarized with all experimental procedures. Subsequently, all measures were collected on a single occasion in a quiet, dimly lit and environmentally controlled room between 7am and 10am. Participants fasted for 12h, consuming only water, and refraining from supplement intake that morning. Participants also avoided strenuous physical activity and alcohol for 24 h prior to experimentation. Prior to measurement commencement, participants rested quietly in the supine position for 20-min, with both arms at heart level and stretched at a right angle.<sup>11</sup> The experimental arm was supported on a table with an adjustable height and tilting surface, and the control arm was fixed at heart level.

The experimental timeline is depicted in **Figure 1**. For each participant, measurements were made with the experimental arm in three positions: heart level (0°), -30° heart level, and +30° heart level, separated by 5 min rest prior to measurements. Re-positioning to +/- 30° heart level was randomized, using two sets of 10 unique numbers generated from a number range of 1-20 ([www.randomizer.org](http://www.randomizer.org)). At each experimental arm position PWA assessments were simultaneously made on both arms. A control arm was used to determine whether any changes in the estimated central BP waveform were real or an

artifact of local hemodynamic manipulation. Experimental arm local hemodynamic changes were measured using Duplex Doppler ultrasound. Lastly, to confirm central hemodynamic stability, continuous wave ultrasound was used to obtain trans-aortic Doppler flow profiles. All measurements were made in triplicate, with one min rest between readings, and the closest two recordings were averaged.

#### PULSE WAVE ANALYSIS: EXPERIMENTAL ARM

Oscillometric pressure waveforms were recorded by a single operator using a SphygmoCor XCEL device (AtCor Medical, Sydney, Australia). An appropriately sized cuff was selected according to manufacturer guidelines (small adult 17–25 cm, adult 23–33 cm, large adult 31–40 cm) and placed around the left upper arm. Each measurement cycle lasted ~60 s. The upper arm cuff was initially inflated to measure brachial systolic (SBP) and diastolic (DBP) blood pressure, and then reinflated 5 s later to 10 mmHg below DBP to acquire a volumetric displacement signal for 10 s.<sup>12</sup> The brachial waveforms were calibrated using the cuff-measured SBP and DBP, and mean arterial pressure (MAP) was derived by integrating the area under the curve. A corresponding aortic pressure waveform was generated using a validated proprietary transfer function and calibrated using DBP and MAP.<sup>12</sup> The aortic waveform was used to derive central: cSBP, diastolic BP (cDBP), pulse pressure (cPP), pulse pressure amplitude (PPamp), augmentation pressure (cAP), cAIx, cAIx normalized to a heart rate of 75 bpm (cAIx@75), aortic backward pressure wave (Pb), aortic forward pressure wave (Pf), and reflection magnitude (RM).



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135 The PPamp is the ratio of peripheral pulse pressure to cPP multiplied by 100. The cAlx is  
 136 defined as the cAP expressed as a percentage of cPP, where cAP is defined as the  
 137 maximum cSBP minus the pressure at the inflection point. The Pf and Pb wave pressures  
 138 were determined by assuming a triangular flow wave.<sup>13</sup> This method creates a triangular-  
 139 shaped flow wave by matching the start, peak, and end of the flow wave to the timings of  
 140 the foot, inflection point, and incisura of the aortic pressure wave. The RM was calculated  
 141 as Pb/Pf.

142

#### 143 PULSE WAVE ANALYSIS: CONTROL ARM

144 Oscillometric pressure waveforms were recorded on the upper arm using an Oscar 2  
 145 (SunTech Medical, Morrisville, USA) and a cuff identical in size to the one used for the  
 146 XCEL device. The Oscar 2 incorporates the same patented BP model as the XCEL, and has  
 147 been validated according to the British Hypertension Society and the European Society of  
 148 Hypertension International Protocol.<sup>14,15</sup> Measurements included cSBP, cDBP, cPP, PPamp,  
 149 cAP, cAlx, and cAlx@75. The Oscar 2 does not currently measure Pb, Pf or RM.

150

#### 151 DUPLEX DOPPLER ULTRASOUND: EXPERIMENTAL ARM

152 A 11-2 mHz linear array probe (LOGIQ P6, GE Healthcare, Wauwatosa, USA) was used to  
 153 record brachial artery brightness-mode images and pulsed doppler waveforms.<sup>16,17</sup> The  
 154 ultrasound probe was placed on the brachial artery, 5-10 cm proximal to the antecubital

fossa. The isonation angle was kept constant between 45° and 60° and the sample volume included most of the vessel. Three 10 s video recordings were taken at 30 Hz using an external video capture system (AV.io HD Frame Grabber, Epiphan Video, CA), during which the participant was asked to hold their breath without prior inhalation.

The captured videos were analysed offline using specialized image analysis software (FMD Studio®, QUIPU, Italy), which outsourced (30 Hz) brachial artery diameters as well as antegrade and retrograde blood velocities. Blood velocities were analysed by tracing the peak envelope of the spectral waveform. Subsequently, custom-written Visual Basic code was used to fit peaks and troughs to the diameter waveforms to calculate diastolic ( $D_d$ ), systolic ( $D_s$ ), mean diameters ( $D_{mean}$ ), and distention (Dist.).<sup>18,19</sup> The Visual Basic software also automated the calculation of study outcomes: mean blood velocity ( $V_{mean}$ ), diastolic blood velocity ( $V_{dia}$ ), systolic blood velocity ( $V_{sys}$ ), retrograde blood velocity ( $V_{neg}$ ), mean blood flow ( $BF_{mean}$ ), change in blood flow over the cardiac cycle ( $\Delta BF$ ), shear rate, oscillatory index (OI), conductance, and local arterial stiffness (beta-stiffness index [ $\beta$ ]). Shear rate ( $s^{-1}$ ) was calculated as  $4 \times \text{mean velocity} / \text{diameter}$ , blood flow as  $\text{mean vessel area} \times \text{mean blood velocity} \times 60$ , conductance ( $ml \cdot min^{-1} \cdot mmHg$ ) as  $\text{mean blood flow} / \text{MAP}$ , and OI as  $\text{retrograde shear rate} / (\text{antegrade shear rate} + \text{retrograde shear}) \times 100$ .<sup>20</sup> The values for OI range from 0 to 50, where zero is strictly antegrade shear and 50 is purely oscillatory. The  $\beta$  was calculated as  $\ln(SBP/DBP) / [(D_s - D_d) / D_d]$ .

## CONTINUOUS-WAVE ULTRASOUND: TRANS-AORTIC

Stroke volume (SV), cardiac output (CO) and systemic vascular resistance (SVR) were measured at each arm position using continuous-wave Doppler ultrasound (USCOM 1A, Uscom, Sydney, Australia). A single operator placed a 3.3MHz continuous-wave probe over the acoustic window at the level of the sternal notch to obtain trans-aortic Doppler flow profiles. Three 12 s recordings were taken for each arm position and the closest two were averaged. The BPs from the control arm were used to calculate SVR.

## SAMPLE SIZE

Sample size calculations were based on cAlx, which has lower between-day reliability than the primary outcome, cSBP,<sup>6</sup> and is similarly reliable to Pb.<sup>7</sup> The mean change in derived cAlx reported following upper-limb tilt (+30° or -30°) from heart level is approximately 10% (data estimated from pooled data), but the smallest change reported is approximately 5%.<sup>3</sup> The typical error of cAlx measurement using the SpygmoCor XCEL is 5.2% for uncontrolled conditions.<sup>6</sup> Using a conservative typical change during arm tilt of 5% and a conservative typical error of 5.2%, with the maximum chances of a Type I error set at 5%, and a Type II error of 20%, we estimated the approximate number of participants required at 19.<sup>21</sup> To permit even distribution by sex, the sample size was inflated to 20.

## STATISTICS

Statistical analyses were performed using Statistical Package for Social Sciences version 25 (SPSS, Inc., Chicago, Illinois) and Hierarchical Linear Modelling-6 (Scientific Software International, Inc., Lincolnwood, Illinois). Statistical significance was defined as  $p < 0.05$  (two tailed). To test for the main effect of arm position on each outcome analysis of variance (ANOVA) for repeated measurement was used, after verification of the normality of distributions. Homogeneity of variance was evaluated using Mauchly's test of sphericity and, when violated, the Greenhouse-Geisser adjustment was used. In the event of a significant main effect, pairwise comparisons against heart level measurements were conducted. Effect sizes (ES) are reported using partial eta-squared ( $\eta^2_p$ ), where 0.01, 0.06, and 0.14 represent a small, medium, and large effect, respectively.<sup>22</sup>

Hierarchical Linear Modelling (HLM) was used to address the final objective, i.e., associations between change in estimated cSBP and arterial wave reflection and change in local artery hemodynamics. Three models were run for each analysis. Model 1 specified arm tilting (arm position relative to heart level), and was used to estimate measurement reliability.<sup>23</sup> Model 2 specified the predictor which most strongly associated with outcome, as a group-centered to determine whether change in this variable helps to explain within-subject variation for change in the outcome. Model 3 specified the next strongest predictor variable as a group-centered covariate.

## RESULTS

Local and central hemodynamic data for the experimental arm were successfully collected from all 20 participants (26.7 y [SD 5.2], 50% women, BMI 24.0 kg/m<sup>2</sup> [SD 2.8]). For the control arm, PWA measurements were unsuccessful for one participant for an unknown reason. Additionally, ultrasound measures were unsuccessful on one participant due to poor video quality. These two participants were similar to the remainder of the population in terms of demographics and baseline hemodynamic measures.

## EXPERIMENTAL ARM MEASUREMENTS

### Pulse Wave Analysis

All measurements are reported in **Table 1**. We observed no significant main effects of arm tilting on HR, PPamp, Pb, Pf or RM. However, there were large (ES=0.27-0.82), significant main effects of arm tilting on MAP, DBP, SBP, cSBP, cAP, cAlx, and cAlx75. Pairwise contrasts indicate that maneuvering the arm 30° above heart level resulted in significantly decreased MAP, DBP, SBP, cSBP, but non-significant changes in cAP, cAlx, and cAlx75. Conversely, positioning the arm 30° below heart level led to significantly increased MAP, DBP, SBP, cSBP, significantly decreased cAP and cAlx, and resulted in a non-significant decrease in cAlx75.

### Ultrasound

We observed non-significant main effects for  $V_{\text{mean}}$ ,  $BF_{\text{mean}}$ , conductance, and shear rate. However, there were large (ES=0.20-0.60), significant main effects for distension,  $\theta$ ,  $V_{\text{dia}}$ ,

$V_{sys}$ ,  $V_{neg}$ ,  $\Delta BF$  and  $OI$ . Pairwise contrasts indicate that maneuvering the arm  $30^\circ$  above heart level resulted in significantly increased  $V_{dia}$ ,  $OI$  and  $V_{neg}$ , and a non-significant change in  $\beta$ ,  $Dist$ ,  $V_{sys}$ , and  $\Delta BF$ . Conversely, positioning the arm  $30^\circ$  below heart level led to significantly increased  $\beta$ , significantly decreased  $V_{sys}$  and  $\Delta BF$ , and had a non-significant effect on distention,  $V_{mean}$ , and  $V_{neg}$ .

#### CONTROL MEASUREMENTS: CONTROL ARM AND TRANS-AORTIC

All measurements are reported in **Table 2**. When the experimental arm was repositioned, we observed no significant main effects for HR, SBP, cSBP,  $PP_{amp}$ , or cAP. However, there were large ( $ES=0.19-0.32$ ) and significant main effects for MAP, DBP, cAIx and cAIx75. Pairwise contrasts indicate that maneuvering the experimental arm  $30^\circ$  above heart level resulted in significantly increased MAP and DBP and significantly decreased cAIx and cAIx75 in the control arm. Positioning the experimental arm  $30^\circ$  below heart level also led to significantly increased MAP and DBP in the control arm but had a non-significant effect on cAIx and cAIx75.

We observed no significant main effects for CO, SV or HR. However, there was a large ( $ES=0.25$ ) and significant main effect for SVR. Pairwise contrasts indicate that maneuvering arm  $30^\circ$  above heart level significantly increased SVR, whereas positioning the arm  $30^\circ$  below heart level had a non-significant effect on SVR.

## ASSOCIATIONS BETWEEN CENTRAL AND LOCAL HEMODYNAMIC

### MEASURES

Data from 19 participant, for a total of 57 data points were available for the HLM models. Only cSBP and cAIx were modelled as these outcomes were influenced by arm tilting, whereas Pb was not. The ultrasound-derived local hemodynamic measures, which significantly changed in response to arm tilting, were considered for HLM analysis. Initially, each local hemodynamic variable was independently associated with cSBP and cAIx, using HLM. The variables which were significantly associated with cSBP or cAIx were specified as subject-centered in order of strength of association.  $V_{\text{sys}}$  and  $D_{\text{mean}}$ , and  $V_{\text{neg}}$  and  $\theta$  were found to be significant independent predictors of cSBP and cAIx, respectively. The HLM models for cSBP are reported in **Table 3**. Model 3 shows that, after controlling for  $V_{\text{sys}}$  and  $V_{\text{mean}}$ , each 10° elevation in arm position, beginning at -30°, resulted in a 2.05 mmHg decrease in cSBP. The HLM models for cAIx are reported in **Table 4**. After controlling for  $V_{\text{neg}}$  and  $\theta$ , each 10° elevation in arm position, beginning at -30°, resulted in a 0.16% increase in cAIx.

### DISCUSSION

Non-invasive PWA devices have been demonstrated to provide reliable<sup>6–8</sup> and valid<sup>24,25</sup> estimates of central hemodynamic properties, and the prognostic value of cSBP has been recognized by expert consensus.<sup>2,26,27</sup> The current findings do not invalidate PWA devices but do suggest that the accuracy of the estimated aortic pressure waveform is dependent

on stable local hemodynamics at the assessment site. Local hemodynamic manipulation, induced through arm tilting, had a large effect on estimated cSBP and cAIx, but not Pb. We further add to the extant literature by observing a direct association of cSBP and cAIx with local hemodynamic factors. These findings provide mechanistic insight into the factors influencing the accuracy of PWA.

## STRENGTHS AND LIMITATIONS

The strengths and limitations of this study need to be addressed to best contextualize the findings. A major strength is the simultaneous measurement of peripheral and central hemodynamic variables. Additionally, the homogenous group of young, healthy participant permitted measurement of sensitive changes in hemodynamic variables without the confounding influence of age or disease-status. However, there were some limitations. While our sample population did permit optimal signal to noise, further study with older and clinical populations is required to better generalize the findings. For example, in older participant sarterial wave reflection has been demonstrated to be less sensitive to change with arm tilting,<sup>3</sup> in hypertensive participants the relationship between BP and arterial stiffness may be different,<sup>28</sup> and the effects of sex are unknown. Additionally, we did not control for vasomotor changes resulting from arm movement.<sup>29</sup> However, the arm was moved slowly and was fully supported at all times, we did allow a 5-min rest interval, and measurements were taken in triplicate. Lastly, the current study utilized an oscillometric device (XCEL) to estimate the aortic pressure waveform from the



brachial artery, and SphygmoCor originally developed a proprietary transfer function for use with radial artery tonometry. However, a proprietary transfer function has been developed specifically for the XCEL,<sup>12</sup> and central hemodynamic outcomes derived from the XCEL have been validated using both radial artery tonometry<sup>12,30,31</sup> and high-fidelity invasive catheterization.<sup>24,25</sup>

### CENTRAL SYSTOLIC BLOOD PRESSURE

The overall displacement in peripheral SBP in the experimental arm was 15 mmHg, which is comparable to the 20 mmHg displacement reported by Pucci *et al.*<sup>3</sup> Of particular interest, the PP amplification (ratio of central to peripheral PP) did not change with arm tilting for either study, suggesting that local pressure wave transmission directly influences the estimated central waveform. The estimated central waveform was similarly affected in both studies despite Pucci *et al.*<sup>3</sup> recording the peripheral waveform at the radial artery with tonometry, and the current study estimating the peripheral waveform at the brachial artery with oscillometry. Further, the changes to local and estimated cSBP occurred despite no changes to SBP or cSBP estimated from the control arm. Herein, we extend the findings of Pucci *et al.*<sup>3</sup> by reporting that change in cSBP was found to be associated with local hemodynamic changes, including brachial artery systolic blood velocity and mean diameter.

Brachial artery systolic blood velocity was particularly susceptible to the arm being lowered, whereas brachial artery mean diameter was most susceptible to raising the arm. When lowering the arm, systolic blood velocity decreased despite no change in mean velocity, indicating that the shape of the velocity profile was altered rather than the overall volume of blood velocity. The change in systolic blood velocity shape may have been indicative of decreased downstream resistance as a result of blood pooling.<sup>19,32</sup> The decreased downstream resistance may have directly influenced cSBP; however, decreased peripheral resistance would be expected to decrease cSBP.<sup>33</sup> Alternatively, the altered systolic blood velocity may indicate mismatched pulsatile-pressure-flow relations.<sup>33,34</sup> In turn, mean diameter is an indicator of the tone of the vessel, and a major determinant of local BP.<sup>33</sup> However, mean diameter also plays an important general role in the local hemodynamic environment, including arterial stiffness and the blood velocity profile, and change in this variable may be indicative of more general change to the local environment. This may explain why, despite being associated with change in cSBP, specifying mean diameter in the hierarchical linear model did not reduce the change in cSBP with arm tilting.

### ARTERIAL WAVE REFLECTION

In line with our BP findings, cAIx in the experimental arm changed similarly to that of Pucci *et al.*<sup>3</sup> cAIx increased when the arm was raised (albeit not significantly in the current study), and decreased when the arm was lowered. Contrary to Pucci *et al.*,<sup>3</sup> we found that

cAlx significantly decreased (-4.7%) in the contralateral arm, predominantly when the experimental arm was raised. We further extend the findings of Pucci *et al*<sup>3</sup> by reporting that (i) change in experimental arm cAlx was found to be associated with change in brachial artery retrograde blood velocity and brachial arterial stiffness, and (ii) Pb did not significantly change with arm tilting.

Antegrade blood velocity was particularly susceptible to the arm being raised, whereas brachial arterial stiffness was specifically susceptible to the arm being lowered. Antegrade blood velocity may have directly influenced the shape of the local pressure waveform, or may have simply been the consequence of increased downstream vascular resistance.<sup>32</sup> Considering the changes in antegrade blood velocity were small, the later explanation is more likely. Interestingly, brachial arterial stiffness increased with arm lowering while the cAlx decreased, which is opposite to what was expected. As such, perhaps it is not surprising that while both antegrade blood velocity and brachial arterial stiffness did decrease the hierarchical linear modelling estimate for change in cAlx with arm tilting, the standard error for the estimate did not decrease and nor did the residual (within-subject) variance. This indicates that while antegrade blood velocity and brachial arterial stiffness are associated with cAlx, other factors do contribute to a change in cAlx. One explanation is that at least part of the cAlx change is not artificial, and that arm tilting does have a small systemic effect. Indeed, contrary to Pucci *et al*,<sup>3</sup> we observed changes to cAlx in the contralateral arm, and these changes are supported by small but robust changes in

systemic vascular resistance. Pucci *et al*<sup>3</sup> may not have observed changes to cAIx in the contralateral arm as a result of the wide age range of study subjects.

In contrast to cAIx, Pb did not significantly change in response to arm tilting. This finding supports previous work from our group indicating that, when compared to Pb, cAIx is more prone to error with change in body posture.<sup>6-8</sup> Two potential sources of error may have limited the estimation of arterial wave reflections using cAIx: (i) the reflected wave transit time, and (ii) the generalized transfer function used to generate the aortic pressure waveform. (i) The cAIx is affected by the reflected wave transit time, which is influenced by the reflected wave timing, amplitude, and ventricular function, and which are known to be influenced by a number of factors, including heart rate.<sup>4</sup> However, heart rate was not significantly affected by arm tilting. Alternatively, (ii) the generalized transfer function may less truly reproduce the high-frequency components required for cAIx computation than it does the low-frequency pressure harmonics required for Pb and Pf computation.<sup>35</sup>

## IMPLICATIONS

Central BP measurement prognostic value has been recognized by expert consensus, and is gaining traction as a clinical outcome.<sup>2,26,27</sup> The traction is supported by the validation of diagnostic thresholds,<sup>36</sup> and evidence demonstrating that monitoring central BP, as opposed to conventional peripheral BP, aided in the management of hypertension, leading to decreased medication use without adverse effects on left ventricular mass.<sup>37</sup>

However, as with peripheral BP measures, central BP and arterial wave reflection are currently measured in both supine and seated positions, with the arm resting at various heights.<sup>38</sup> Findings from the current study, along with previous work from our group and others,<sup>3,6–9</sup> suggest that lack of procedural standardization may have meaningful implications for patient management.

Our findings may have particular relevance to 24-h ambulatory central BP devices, as changes in body posture and arm position may confound the accuracy of readings. As such, it is recommended that participants are instructed to remain supine during key measurement periods. Additionally, the current findings do indicate that Pb may be a more robust measure of arterial wave reflection than cAlx. Two large prospective studies<sup>39,40</sup> suggest that wave separation analysis may be superior to cAlx as a subclinical marker of cardiovascular disease – one reporting that Pb better predicts 15-year cardiovascular mortality than cAlx,<sup>39</sup> the other that reflection magnitude (Pb/Pf) better predicts cardiovascular events than cAlx.<sup>40</sup> Whether or not Pb is a superior ambulatory measure than cAlx warrants further attention.

## CONCLUSIONS

This study investigated whether changes to the local hemodynamic environment, induced through arm tilting, affect estimated cSBP and indices of arterial wave reflection. Arm tilting had no effect on Pb. However, arm tilting did have a large effect on estimated cSBP

and cAIx in the experimental arm, but not in the control arm. The changes in cSBP and cAIx were partially explained by changes in local hemodynamic factors. These findings do not invalidate PWA devices but do suggest that the accuracy of the estimated aortic pressure waveform is dependent on stable peripheral hemodynamics at the measurement site.

#### **ACKNOWLEDGEMENTS**

None.

#### **CONFLICT OF INTEREST**

The authors declare that they have no conflict of interest

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## FIGURES

**Figure 1.** Study design. The experimental arm was passively repositioned three times (heart level [0°], below heart level [-30°], below heart level [+30°]), while the control arm remained fixed at heart level. Following repositioning a 5 min rest preceded measurements. Measurements on the experimental arm included pulse wave analysis (PWA, XCEL) and duplex Doppler ultrasound (US<sub>DD</sub>). On the control arm PWA (Oscar 2) measures were taken at the same time as experimental arm PWA measures. Lastly, for each arm position a continuous wave ultrasound (US<sub>CW</sub>) probe was placed at the level of the sternal notch to obtain trans-aortic Doppler flow profiles. All measurements were made in triplicate.

## TABLES

**Table 1.** Hemodynamic measures on the experimental arm (n=20)

Abbreviations: ES, effect size (partial eta squared), where 0.01, 0.06, and 0.14 represent a small, medium, and large effect, respectively; Cont., contrast; LCI, lower confidence interval (95%); UCI, upper confidence interval (95%);  $\Delta$ BF, change in blood flow (systole – diastole); cAIx, central augmentation index; cAIx75, cAIx normalize to a heart rate of 75 bpm; cAP, central augmentation pressure;  $\beta$ , beta index stiffness; BF<sub>mean</sub>, mean blood flow; Cond., conductance; cSBP, central systolic blood pressure; DBP, diastolic blood pressure; Dist, distention (brachial diameter change); D<sub>mean</sub>, mean arterial (brachial) diameter; MAP, mean arterial blood pressure; Pf, aortic forward pressure wave; Pb, aortic backward pressure wave; PP<sub>amp</sub>, pulse pressure amplitude; OI, oscillatory index; RM, reflection magnitude; SBP, systolic blood pressure; shear, shear rate; V<sub>dia</sub>, diastolic

blood velocity;  $V_{\text{mean}}$ , mean blood velocity;  $V_{\text{neg}}$ , negative (retrograde) blood velocity;  $V_{\text{sys}}$ , systolic blood velocity

**Table 2.** Control measurements: contralateral arm hemodynamic measures and central output (n=19)

Abbreviations: cAlx, central augmentation index, Alx75, cAlx normalize to a heart rate of 75 bpm; cAP, central augmentation pressure; CO, cardiac output; cSBP, central systolic blood pressure; DBP, diastolic blood pressure;  $D_{\text{mean}}$ , mean arterial (brachial) diameter; HR, heart rate;  $PP_{\text{amp}}$ , pulse pressure amplitude; MAP, mean arterial blood pressure; SBP, systolic blood pressure; SV, stroke volume; SVR, systemic vascular resistance

**Table 3.** Hierarchical linear modeling estimates for change in central systolic blood pressure (cSBP) with arm tilting (n=57 data points)

Note: the slopes are reported as a  $10^\circ$ , rather than  $1^\circ$  or  $30^\circ$  change to aid interpretation. Measurements were only conducted at  $-30^\circ$ ,  $0^\circ$  and  $30^\circ$ .

Abbreviations:  $D_{\text{mean}}$ , brachial artery mean diameter;  $V_{\text{sys}}$ , systolic blood velocity;

**Table 4.** Hierarchical linear modeling estimates for change in central augmentation index (cAlx) with arm tilting (n=20)

Note: the slopes are reported as a  $10^\circ$ , rather than  $1^\circ$  or  $30^\circ$  change to aid interpretation. Measurements were only conducted at  $-30^\circ$ ,  $0^\circ$  and  $30^\circ$ .

Abbreviations:  $\beta$ , beta stiffness in the brachial artery;  $V_{\text{neg}}$ , negative (retrograde), blood velocity



569 **Table 1.** Hemodynamic measures on the experimental arm (n=57 data points)

|                             | 30° Above |     | Heart Level |     | 30° Below |     | Significance |      | 30° Above Heart |      |      |       | 30° Below Heart |      |       |       |
|-----------------------------|-----------|-----|-------------|-----|-----------|-----|--------------|------|-----------------|------|------|-------|-----------------|------|-------|-------|
|                             | X         | SD  | X           | SD  | X         | SD  | P            | ES   | Cont.           | LCI  | UCI  | P     | Cont.           | LCI  | UCI   | P     |
| MAP (mmHg)                  | 77.3      | 5.6 | 82.2        | 5.4 | 91.9      | 6.0 | <0.001       | 0.82 | -4.64           | -7.6 | -1.7 | 0.002 | 9.76            | 12   | 7.2   | 0.000 |
| DBP (mmHg)                  | 61.5      | 6.4 | 66.1        | 5.9 | 74.9      | 6.5 | <0.001       | 0.80 | -4.70           | -7.5 | -1.8 | 0.001 | -13.3           | -17  | -9.9  | 0.000 |
| SBP (mmHg)                  | 110       | 5.3 | 114         | 6.3 | 125       | 7.7 | <0.001       | 0.75 | -4.38           | -7.5 | -1.3 | 0.005 | 10.4            | 14   | 6.5   | 0.000 |
| cSBP (mmHg)                 | 94.5      | 5.7 | 99.5        | 5.7 | 109       | 6.9 | <0.001       | 0.81 | -4.90           | -7.8 | -2.0 | 0.001 | 9.45            | 12   | 6.4   | 0.000 |
| PP <sub>amp</sub> (ratio)   | 1.46      | 0.6 | 1.45        | 0.9 | 1.47      | 0.9 | 0.199        | 0.08 | 0.16            | -0.1 | 0.4  | 0.430 | 0.27            | -0.1 | 0.7   | 0.301 |
| cAP (mmHg)                  | 0.68      | 2.4 | 0.48        | 3.3 | -1.55     | 4.2 | 0.002        | 0.29 | 0.20            | -1.2 | 1.6  | 1.000 | -2.15           | -4.2 | -0.2  | 0.033 |
| cAix (%)                    | 1.55      | 8.8 | 1.45        | 9.4 | -4.63     | 12  | 0.002        | 0.27 | 0.10            | -3.6 | 3.8  | 1.000 | -6.20           | -12  | -0.7  | 0.023 |
| cAix75 (%)                  | -8.05     | 10  | -9.00       | 13  | -15.1     | 15  | 0.005        | 0.27 | 0.56            | -3.5 | 4.6  | 1.000 | -6.22           | -13  | 0.4   | 0.070 |
| Pb (mmHg)                   | 11.1      | 2.0 | 11.1        | 1.4 | 11.5      | 1.9 | 0.338        | 0.06 | 0.00            | -0.8 | 0.8  | 1.000 | 0.45            | -0.4 | 1.3   | 0.528 |
| Pf (mmHg)                   | 25.0      | 2.3 | 24.8        | 2.6 | 25.3      | 3.5 | 0.809        | 0.01 | 0.20            | -1.5 | 1.9  | 1.000 | 0.50            | -1.6 | 2.6   | 1.000 |
| RM (%)                      | 43.4      | 6.1 | 45.1        | 6.6 | 43.9      | 4.7 | 0.352        | 0.05 | 1.75            | -5.9 | 2.4  | 0.840 | -1.25           | -4.6 | 2.1   | 1.000 |
| HR (bpm)                    | 52.2      | 8.5 | 52.5        | 9.3 | 51.6      | 7.9 | 0.651        | 0.02 | 0.30            | -2.4 | 1.8  | 1.000 | -0.88           | -3.3 | 1.5   | 1.000 |
| D <sub>mean</sub> (mm)      | 3.68      | 0.7 | 3.58        | 0.8 | 3.61      | 0.8 | 0.075        | 0.26 | 0.11            | 0.0  | 0.2  | 0.105 | 0.01            | -0.1 | 0.1   | 1.000 |
| Dist (mm)                   | 0.08      | 0.0 | 0.07        | 0.0 | 0.05      | 0.0 | 0.002        | 0.29 | 0.01            | 0.0  | 0.0  | 0.537 | -0.02           | 0.0  | 0.0   | 0.085 |
| $\beta$                     | 29.3      | 9.2 | 28.5        | 8.0 | 39.0      | 13  | 0.002        | 0.30 | 0.77            | -6.0 | 7.5  | 1.000 | 10.5            | 3.3  | 18    | 0.004 |
| V <sub>dia</sub> (cm/s)     | 1.21      | 1.4 | 0.00        | 0.0 | 0.00      | 0.0 | <0.001       | 0.44 | 1.21            | 0.4  | 2.1  | 0.005 | na              |      |       |       |
| V <sub>sys</sub> (cm/s)     | 84.8      | 15  | 81.7        | 16  | 62.9      | 14  | <0.001       | 0.72 | 3.10            | -2.9 | 9.1  | 0.564 | -18.8           | -26  | -12   | 0.000 |
| V <sub>mean</sub> (cm/s)    | 10.0      | 2.5 | 11.1        | 2.8 | 10.9      | 14  | 0.893        | 0.01 | -1.08           | -2.3 | 0.2  | 0.111 | -0.16           | -7.8 | 7.5   | 1.000 |
| V <sub>neg</sub> (cm/s)     | -3.41     | 2.6 | -1.96       | 1.4 | -1.80     | 1.4 | 0.000        | 0.36 | -1.45           | -2.6 | -0.3 | 0.011 | 0.16            | -0.5 | 0.8   | 1.000 |
| BF <sub>mean</sub> (ml/min) | 62.3      | 27  | 63.9        | 23  | 57.5      | 48  | 0.801        | 0.01 | -1.55           | -10  | 7.3  | 1.000 | -6.33           | -37  | 24    | 1.000 |
| $\Delta$ BF (ml/min)        | 546       | 213 | 510         | 225 | 386       | 154 | <0.001       | 0.60 | -36.3           | -19  | 92   | 0.300 | -123            | -187 | -60.1 | 0.000 |
| Cond. (ml/min/mmHg)         | 0.81      | 0   | 0.78        | 0.3 | 0.63      | 0.6 | 0.275        | 0.07 | 0.03            | -0.1 | 0.1  | 1.000 | -0.16           | -0.5 | 0.2   | 0.837 |
| Shear (s <sup>-1</sup> )    | 117       | 45  | 131         | 52  | 138       | 198 | 0.833        | 0.01 | -20.2           | -26  | -1.7 | 0.022 | 6.42            | -100 | 113   | 1.000 |
| OI (ratio)                  | 23.8      | 12  | 14.3        | 6.5 | 15.5      | 9.5 | 0.001        | 0.33 | 9.47            | 2.8  | 16   | 0.005 | 1.20            | -3.8 | 6.2   | 1.000 |

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577 **Table 2.** Control measurements: contralateral arm hemodynamic measures and central output (n=19)

|                               | 30° Above |     | Heart Level |     | 30° Below |     | Significance |      | 30° Above Heart |       |      |       | 30° Below Heart |      |      |       |
|-------------------------------|-----------|-----|-------------|-----|-----------|-----|--------------|------|-----------------|-------|------|-------|-----------------|------|------|-------|
|                               | X         | SD  | X           | SD  | X         | SD  | P            | ES   | Cont.           | LCI   | UCI  | P     | Cont.           | LCI  | UCI  | P     |
| MAP (mmHg)                    | 82.1      | 6.8 | 79.9        | 5.8 | 81.9      | 6.3 | 0.002        | 0.32 | 2.26            | 0.6   | 3.9  | 0.006 | 1.9             | 0.5  | 3.4  | 0.007 |
| DBP (mmHg)                    | 64.6      | 5.6 | 62.2        | 5.9 | 64.7      | 6.2 | 0.002        | 0.30 | 2.30            | 0.8   | 3.9  | 0.003 | 2.5             | 0.4  | 4.6  | 0.020 |
| SBP (mmHg)                    | 117       | 9.7 | 115         | 8.6 | 117       | 8.6 | 0.166        | 0.10 | 1.50            | -0.9  | 3.8  | 0.345 | 1.4             | -0.3 | 3.2  | 0.139 |
| cSBP (mmHg)                   | 103       | 9.3 | 102         | 7.4 | 103       | 8.2 | 0.164        | 0.11 | 1.26            | -1.0  | 3.6  | 0.493 | -1.2            | -0.7 | 3.0  | 0.360 |
| PP <sub>amp</sub> (ratio)     | 1.39      | 0.8 | 1.37        | 0.7 | 1.38      | 0.8 | 0.270        | 0.07 | 0.19            | -0.0  | 0.5  | 0.274 | 0.0             | -0.1 | -0.3 | 0.955 |
| cAP (mmHg)                    | 1.42      | 5.3 | 2.84        | 4.9 | 1.79      | 4.1 | 0.068        | 0.14 | -1.37           | -3.1  | 323  | 0.140 | -1.1            | -2.6 | 0.5  | 0.258 |
| cAix (%)                      | 2.53      | 15  | 7.21        | 12  | 3.26      | 11  | 0.013        | 0.22 | -4.74           | -9.3  | -0.2 | 0.041 | -3.9            | -7.9 | 0.1  | 0.054 |
| cAix75 (%)                    | -8.11     | 17  | -3.00       | 15  | -6.55     | 13  | 0.021        | 0.19 | -5.21           | -10.2 | -0.2 | 0.039 | -3.7            | -8.5 | 1.2  | 0.181 |
| HR <sub>Oscar</sub> (bpm)     | 52.1      | 7.7 | 53.4        | 8.2 | 53.3      | 7.5 | 0.059        | 0.15 | -1.47           | -3.1  | 0.2  | 0.095 | -0.2            | -1.9 | 1.5  | 1.000 |
| HR <sub>USCOM</sub> (bpm)     | 51.8      | 9.3 | 52.3        | 10  | 52.1      | 8.3 | 0.906        | 0.01 | -0.43           | -2.5  | 1.7  | 1.000 | -0.2            | -3.2 | 2.8  | 1.000 |
| CO (l/min)                    | 4.30      | 1.3 | 4.46        | 1.3 | 4.41      | 0.9 | 0.344        | 0.06 | -0.17           | -0.4  | 0.0  | 0.044 | -0.1            | -0.4 | 0.3  | 1.000 |
| SV (mL)                       | 83.1      | 20  | 85.3        | 19  | 85.6      | 19  | 0.171        | 0.09 | -2.25           | -5.8  | 1.3  | 0.335 | 0.2             | -3.5 | 3.9  | 1.000 |
| SVR (d·sec·cm <sup>-5</sup> ) | 1653      | 425 | 1528        | 377 | 1569      | 331 | 0.004        | 0.25 | 125             | 47    | 202  | 0.001 | 41              | -60  | 143  | 0.900 |

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590 **Table 3.** Hierarchical linear modeling estimates for change in central systolic blood pressure (cSBP) with arm tilting (n=20)

|               | Model 1 |    |          | Model 2 |    |          | Model 3 |    |          |
|---------------|---------|----|----------|---------|----|----------|---------|----|----------|
|               | Est.    | SE | <i>P</i> | Est.    | SE | <i>P</i> | Est.    | SE | <i>P</i> |
| Fixed Effects |         |    |          |         |    |          |         |    |          |

|                    |               |       |     |        |       |     |        |       |     |        |  |
|--------------------|---------------|-------|-----|--------|-------|-----|--------|-------|-----|--------|--|
| Intercept (-30°)   | $\theta_{00}$ | 103   | 1.3 | <0.001 | 103   | 1.3 | <0.001 | 103   | 1.3 | <0.001 | Initial cSBP, arm at -30°                |
| Arm Tilt (per 10°) | $\theta_{10}$ | -2.39 | 0.2 | <0.001 | -1.82 | 0.3 | <0.001 | -2.05 | 0.3 | <0.001 | cSBP per 10° degree elevation            |
| $V_{\text{sys}}$   | $\theta_{20}$ |       |     |        | -0.02 | 0.1 | 0.008  | -0.13 | 0.1 | 0.026  | cSBP change per 1 unit $V_{\text{sys}}$  |
| $D_{\text{mean}}$  |               |       |     |        |       |     |        | 8.1   | 4.1 | 0.012  | cSBP change per 1 unit $D_{\text{mean}}$ |
| Random Variance    |               |       |     |        |       |     |        |       |     |        |  |
| Intercept          | $U_{00}$      | 5.33  |     | <0.001 | 5.38  |     | <0.001 | 5.40  |     | <0.001 | Between-subject variance                 |
| Residual           | $E$           | 3.26  |     |        | 2.99  |     | 3.23   | 2.85  |     |        | Within-subject variance                  |



**Table 4.** Hierarchical linear modeling estimates for change in central augmentation index (AIx) with arm tilting (n=20)

|                    |               | Model 1 |      |          | Model 2 |      |          | Model 3 |      |          |  |
|--------------------|---------------|---------|------|----------|---------|------|----------|---------|------|----------|--|
|                    |               | Est.    | SE   | <i>P</i> | Est.    | SE   | <i>P</i> | Est.    | SE   | <i>P</i> |  |
| Fixed Effects      |               |         |      |          |         |      |          |         |      |          |  |
| Intercept (-30°)   | $\theta_{00}$ | 0.91    | 2.22 | 0.686    | 0.91    | 2.22 | 0.686    | 0.91    | 2.22 | 0.686    | Initial <b>cAlx</b> , arm at -30°              |
| Arm Tilt (per 10°) | $\theta_{10}$ | 0.92    | 0.34 | 0.015    | 0.48    | 0.39 | 0.240    | 0.16    | 0.39 | 0.692    | <b>cAlx</b> per 10° degree elevation           |
| $V_{\text{neg}}$   |               |         |      |          | -1.66   | 0.70 | 0.029    | -1.69   | 0.08 | 0.020    | <b>cAlx</b> change per 1 unit $V_{\text{neg}}$ |
| $\theta$           |               |         |      |          |         |      |          | -0.19   | 0.66 | 0.038    | <b>cAlx</b> change per 1 unit $\theta$         |
| Random Variance    |               |         |      |          |         |      |          |         |      |          |  |
| Intercept          | $U_{00}$      | 9.25    |      | <0.001   | 9.22    |      | <0.001   | 9.25    |      | <0.001   | Between-subject variance                       |
| Slope              | $U_{10}$      | 0.97    |      | 0.030    | 0.93    |      | 0.059    | 0.74    |      | 0.298    | Between-subject variance                       |
| Residual           | $E$           | 4.87    |      |          | 5.04    |      |          | 4.93    |      |          | Within-subject variance                        |

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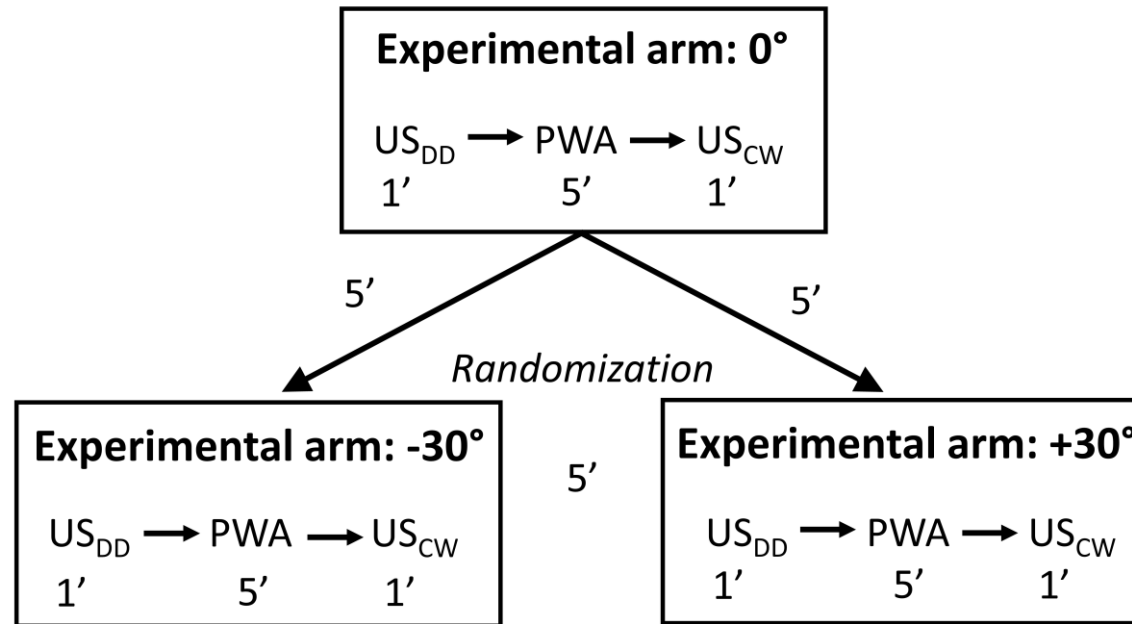
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